THE INFLUENCE OF CERTAIN DRUGS ON CHEYNE-STOKES RESPIRATION.

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THE INFLUENCE OF CERTAIN DRUGS ON CHEYNE-STOKES RESPIRATION.

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IT is not my intention in this paper to enter on any general discussion of Cheyne-Stokes respiration as induced by the action of various drugs; it is, nevertheless, expedient to recall some of the observations which have been made with regard to this subject. In the case narrated by Fräntzel,[1] which gave Traube the opportunity which he utilised to make his classical remarks on the phenomenon, the Cheyne-Stokes type of breathing appeared after the administration of morphine, and similar instances have subsequently been published by Leube,[2] and Bernheim.[3] Biot[4] has observed Cheyne-Stokes respiration follow the use of bromide of potassium, and O'Neill[5] has seen it afte the administration of chloral.

While it is not the aim of the present paper to discuss the appearance of Cheyne-Stokes respiration after the use of certain sedatives, still less is it within its scope to consider the experimental production of periodic breathing, more or less analogous to the morbid symptom. Many experiments of this kind have been published, such as those of Heidenhain, with chloral;[1] Filehne, with ether and chloroform after morphine;[2] François-Franck and Cuffer with urea, carbonate of ammonium, and kreatin;[3] Langendorff with muscarine and digitalin;[4] Solokow and Luchsinger with ether and picrotoxin,[5] and Smirnow with sulphuretted hydrogen.[6]

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[1] *Berliner klinische Wochenschrift*, vol. vi p. 277. 1869.

[2] *Ibid.* vol. vii. p. 177. 1870.

[3] *Gazette Hebdomadaire de Médecine et de Chirurgie.* Deuxième Série, vol. x. pp. 444 and 492. 1873.

[4] *Etude clinique et expérimentale sur la Respiration de Cheyne-Stokes*, p. 59, Paris, 1878.

[5] *The Lancet*, vol. ii. for 1880, p. 691.

Attention must be chiefly directed to the action which has been attributed to nitrite of amyl in Cheyne-Stokes respiration by Filehne.[7] This observer describes a more or less perfect disappearance of the pauses during the inhalation of nitrite of amyl, but unfortunately he does not produce any tracings of the respiration by which the reader of his paper can judge for himself as to the effect of the drug. So far as my own experience is concerned, it by no means agrees with his observations. No doubt in some instances nitrite of amyl has the effect attributed to it by him, and such have come under my own observation. In many cases, on the other hand, the drug in question does not produce the effect described, and before going any further it will be well to narrate a case of this kind.

Miss E. A., housekeeper, aged 60, complains of debility and loss of appetite.

For about three months she has felt a growing sense of weakness, and two months ago, when paying a visit to some friends in Glasgow, she suffered from an attack of palpitation and breathlessness, for which she consulted a medical man, who prescribed digitalis and iron. She has since that time become gradually but steadily worse, and is now confined to bed.

Her *previous health* has been in every way satisfactory.

No facts can be ascertained with regard to her *family history* except that she was left an orphan in early infancy.

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[1] *Archiv für die gesammte Physiologie des Menschen und der Thiere*, vol. iv. p. 554. 1871.

[2] *Berliner klinische Wochenschrift*, vol. xi. pp. 152, 165. 1874.

[3] *Journal de l'Anatomie et de la Physiologie normales et pathologiques de l'Homme et des Animaux*, 1877, p. 545; and *Recherches cliniques et expérimentales sur les Altérations du Sang dans l'Urémie et sur la Pathogénie des Accidents Urémiques—De la Respiration de Cheyne-Stokes dans l'Urémie*, p. 12. Paris, 1878.

[4] *Archiv für Physiologie*, p. 331. 1881.

[5] *Archiv für die gesammte Physiologie des Menschen und der Thiere*, vol. xxiii. p. 283. 1880.

[6] *Centralblatt für die medicinischen Wissenschaften*, vol. 22, p. 641. 1884.

[7] *Berliner klinische Wochenschrift*, vol. xi. pp. 404, 435. 1874.

Her *social condition* has always been comfortable, but she has led an anxious life.

Present condition, November 6th, 1885.—The patient is of medium height, and slender build, with a pallid complexion, tending towards an icteric tint, which is distinctly present in the conjunctiva. The expression is anxious and restless, with staring eyes and dilated pupils. The tongue is covered with a thick yellow fur. The temperature is 98·2° F.

The pulse is 96 per minute, regular, tardy, and of extremely high tension. The radial artery, like the arteries throughout the body, is atheromatous.

The impulse of the heart is somewhat diffuse, and the diastole is accompanied by a sinking inwards of the fourth, fifth, and sixth left intercostal spaces. The apex-beat has its point of maximum intensity in the fifth intercostal space, three-and-a-half inches to the left of the mid-sternal line. The impulse is forcible, and is followed by a well-marked shock accompanying the second sound. No thrill is present.

The first sound is dull and thumping in its character, and in the aortic area the second sound is much accentuated. No murmur is present, but a to-and-fro friction sound is to be heard very distinctly over the base of the heart.

There are no morbid symptoms connected with the lungs.

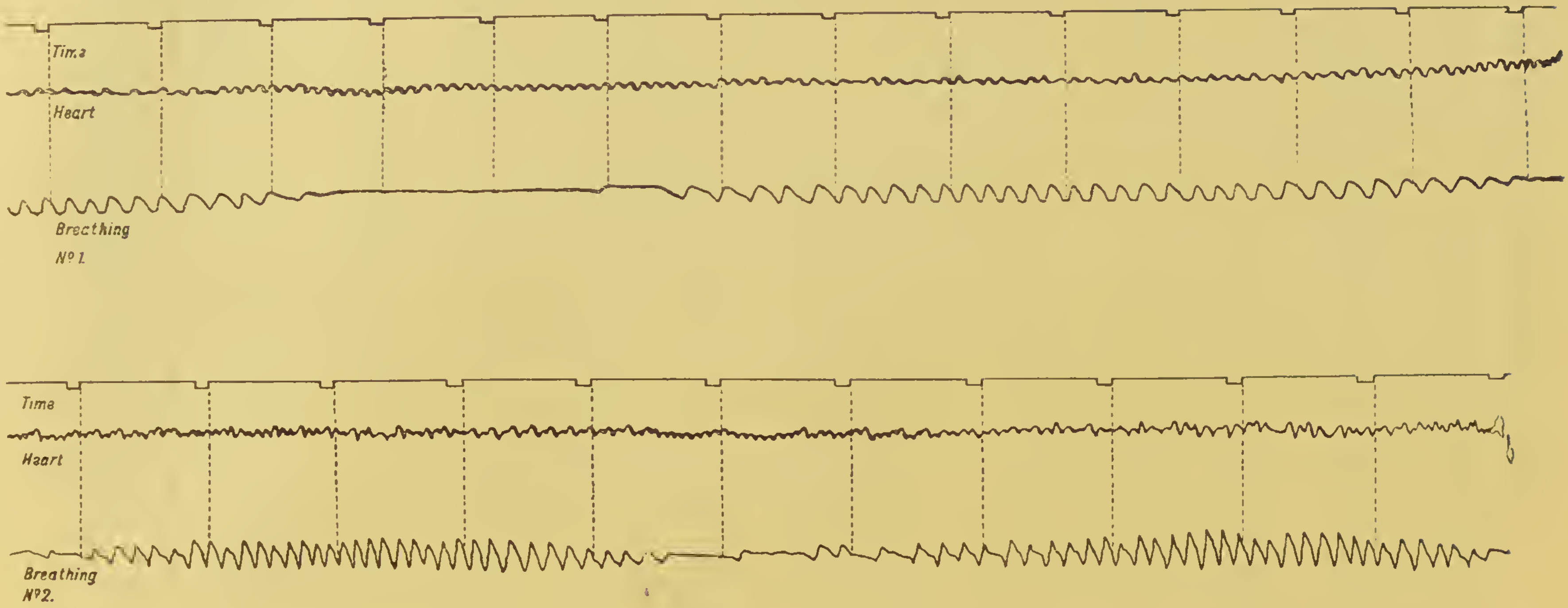
The abdominal organs are confined within their usual limits.

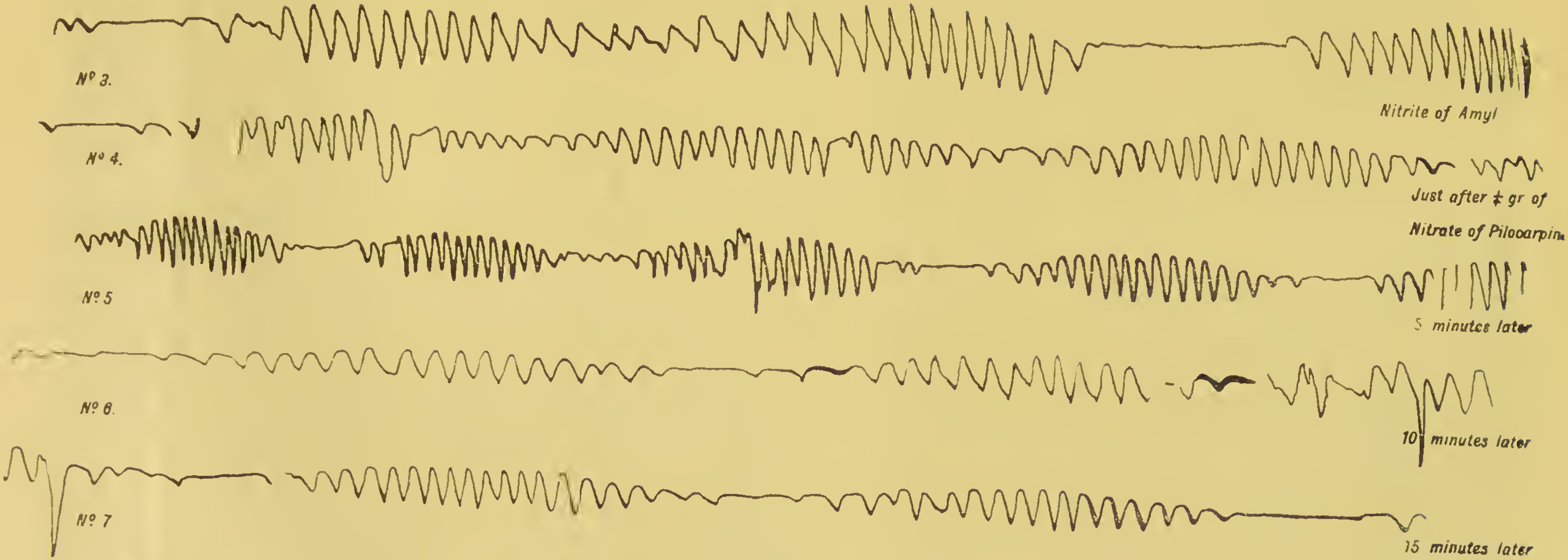
The urine amounts to 25 ounces in twenty-four hours. It is of a pale yellow colour, with a specific gravity of 1013 and a highly acid reaction. It contains about one-fourth of albumen, and 7·5 grains of urea per ounce, or 187·5 grains per day. Microscopically the urine contains broken granular tube-casts and amorphous urates.

The diagnosis was chronic granular kidney, with some roughening of the pericardium as the result of an intercurrent pericarditis.

The patient continued to grow worse in spite of free purgation and other remedies employed, and on the 12th November, after two nights of wandering delirium, Cheyne-Stokes respiration was first observed towards evening, and on the 13th it was fully developed. It was accompanied by most of the appearances usually associated with the symptom, but, as will be seen

CARDIOGRAPHIC AND PNEUMOGRAPHIC TRACINGS IN CHEYNE STOKES RESPIRATION.





The tracings, which are reduced by photography to one half their natural size, are to be read from right to left, and it must be remembered that with Marcy's pneumograph the down strokes represent the inspirations. The time-marker records every fifth second.

from the sequel, there were few variations in the state of the circulation. During the pauses in the breathing the patient lay perfectly motionless with the eyes closed; immediately before the first shallow inspiration of the ascending series of respirations she opened her eyes, and the pupils dilated; as the respiration deepened into dyspnœa her eyes began to roll about, her head was thrown from side to side, and her hands jerked violently in various directions; at the height of the dyspnœa she attempted to rise up in bed and muttered to herself; with the descending series of respirations these phenomena passed away, and when the phase of apnœa was reached she had resumed her motionless attitude. The pupils during the pause were found to be contracted. The pulse varied very slightly, if at all, in its rate throughout the cycle of events, never being less than 24 or more than 26 beats in a quarter of a minute. The tension, so far as could be estimated by the finger, varied still less.

The following day, with the kind assistance of my friend Dr. Alexander James, some tracings were obtained with the cardiograph and the pneumograph, and two of these are given in No. 1 and No. 2. These will show that the number of respirations during the period of breathing was about 35; that the period occupied from 20 to 35 seconds, and the pause from 10 to 15 seconds; and that the apex-beat did not vary much in rate, although the tracing is naturally modified by the heaving of the chest during the period of dyspnœa. In No. 1 the pulsations number about 8 in 5 seconds, and in No. 2 they are about 15. Unfortunately all attempts to obtain a tracing with the sphygmograph failed on account of the jerking which took place during the dyspnœa.

On the 15th the patient was in the same condition, and it was deemed advisable to have recourse to the use of nitrite of amyl. A few drops were administered by inhalation during a period of respiration. The drug at once caused flushing of the face and neck, but did not interfere with the periodic pause in the respiration. Its action was tested by several inhalations during some of which tracings were obtained from the chest. No. 3 shows the curve obtained while the drug was administered, and it proves how slight was the effect of nitrite of amyl on the respiration. The first pause after the use of the drug appeared with its wonted regularity, and before the second pause a period of shallow breathing was found to intervene.

By the 16th the urine had almost become suppressed, and as a last resource it was resolved to employ pilocarpine. One quarter of a grain of the nitrate was administered subcutaneously, and in order to ascertain whether this substance had any effect on the conditions leading to Cheyne-Stokes respiration tracings were taken with the pneumograph. No. 4 was taken immediately after the injection, and therefore before the drug could have caused any effects upon the central nervous system. It shows that three pauses were only present in the form of shallow breathing, but that the fourth pause was clearly marked. No. 5, taken five minutes after the injection, has three complete pauses and one incomplete. No. 6, taken ten minutes after administration, shows very irregular breathing, with pauses intervening between the periods. In No. 7 the breathing is seen to be much in the same state as in No. 1 and No. 2.

On the 16th the power of swallowing was lost and the patient could not be roused; on the 17th she sank steadily, and on the 18th she died. To the last the Cheyne-Stokes respiration was present.

A post-mortem examination of the body was made the day after death by my friend Dr. William Russell, to whose kindness I am indebted for the following description:—

Miss A., æt. 60, died November 18th, 1885. Autopsy, November 19th, twenty-four hours after death.

The body was fairly well nourished. There was a decided icteric tinge in the skin and conjunctivæ. Rigidity and lividity were present. There was no anasarca.

Thorax.—There were 6 oz. of brownish coloured fluid in the right pleural cavity, and 13 oz. of a similar fluid in the left. There were some old pleural adhesions on the right side. Both lungs were congested and œdematous, especially posteriorly. Otherwise they were normal.

The *pericardium* contained no fluid.

Heart.—The heart was firmly contracted. It was considerably enlarged. There was a large deposit of fat on its surface, more especially on the anterior aspect of the right ventricle. The coronary arteries were markedly atheromatous, segments of them being converted into rigid calcareous tubes. The anterior one contained a thrombus not far from its origin, which may have been formed during the process of dying. The muscle of the left ventricle was firm and of a good colour, it varied in thickness from $\frac{3}{8}$ inch to $\frac{1}{2}$ inch; at the apex however it only measured $\frac{1}{4}$ inch, and part of the muscle was replaced by fat. At this point a firm decolorised clot about the size of an almond, and not of very recent formation, had been moulded into a depression in the ventricular wall. The mitral cusps were somewhat thickened, and their free edges slightly retracted. At the junction of the posterior cusps with the cardiac wall there was a thick nodular crescent of calcareous matter over which the endocardium was intact. The *chordæ tendineæ* were also thickened. The aortic valve was competent, but its cusps presented a few small and hard calcareous nodules at their junction with the ventricular wall. The aorta immediately above the valves showed a considerable tract of atheroma. The muscle of the right ventricle was deeply covered with fat, the muscle itself measuring $\frac{1}{8}$ inch in thickness. There was much tough blood clot entangled in the meshes of the *columnæ carneæ* and *musculi papillares*. The tricuspid and pulmonary valves were normal.

Abdomen.—The abdomen contained 20 ozs. of brownish stained serum. The surface of the organs was bile-stained. The intestines in places presented traces of recent peritonitis, their coils being agglutinated to one another by soft lymph.

Kidneys.—Both kidneys were very small, hard, and tough. On section the normal arrangement could be traced with difficulty and only at a few points. There were numerous cysts both on the surface and in the substance of the organs. The cortex was practically obliterated in places. The interlobular vessels were much thickened. The capsules were firmly adherent, and when torn off left a coarsely granular surface. The organs in fact presented the ordinary appearances of advanced atrophic cirrhosis.

Liver.—The liver had some old and firm adhesions at its posterior edge, and at this point there was a depressed cicatrix in the centre, on section of which there was found a calcareous mass twice the size of an almond. Its left edge extended far into the left hypochondrium and was united to the upper border of the spleen by old adhesions. The organ itself was congested and fatty, with a slight increase of its connective tissue arranged in a polylobular fashion.

Spleen.—The spleen was of normal size and somewhat firm consistence.

An examination of the *head* was not permitted.

The point which calls more especially for remark in a clinical respect, in addition to the persistence of the chief symptom, is the fact that the pericardial serous membrane was quite healthy—there were no adhesions, and there was no roughening of the surface. The pericardial friction therefore was caused by the irregular and projecting anterior coronary artery rubbing against the parietal layer of the pericardium.

In this case nitrite of amyl caused no change in the type of the breathing, although, as shown by the flushing of the face and neck, it produced its usual effects on the circulation. The injection of pilocarpine caused a temporary disappearance of the periodic pauses in the respiration.

Now the action of nitrite of amyl in Cheyne-Stokes respiration is a matter of vital importance to the ingenious and elaborate theory advanced by Filehne,[1] to explain the phenomenon. It is not part of the aim of this paper to explain or criticise any of the theories which have been propounded in explanation of the pathogenesis of the type of respiration, but it may be well to mention the chief points of Filehne's theory. He admits that there must be, as Traube[2] described, a lowered irritability of the respiratory centre, but asserts that this is not enough; that the irritability of the respiratory centre must be less than that of the vaso-motor centre, which is, he states, the reverse of the normal relationship existing between them. By this theory it is the stimulation of the vaso-motor centre which leads to stimulation of the respiratory centre by contraction of the arterioles, and consequent anæmia of the latter centre. Nitrite of amyl is thus said by Filehne to arrest the periodic appearance of the pauses by its interference with the vaso-motor mechanism.

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[1] *Loc. cit.* Also, *Revue mensuelle de Médecine et de Chirurgie*, vol. ii. p. 668, 1878, and *Archiv für experimentelle Pathologie und Pharmakologie*, vol. x. p. 442, and vol. xi. p. 45. 1879.

[2] *Loc. cit.* Also, *Gesammelte Beiträge zur Pathologie und Physiologie*, vol. ii p, 852. 1871.

As stated above, it is within my experience that nitrite of amyl in some cases acts in the manner described by Filehne. But what of such cases as that which has just been narrated? In such cases the drug manifestly exerts its action on the vaso-motor apparatus, but in spite of this there is no influence on the respiration, and it is evident that any support which is lent to Filehne's theory by such cases as are susceptible to the action of nitrite of amyl on the respiration is entirely negatived by its failure in other cases.

The influence of such a drug as nitrite of amyl is to be explained in an entirely different manner. When it does exert any influence on the respiration, it does so by means of a stimulant effect on the central nervous structures. Cases have come under my notice in which the inhalation of ether, acting like ammonia, caused the disappearance for a short time of the Cheyne-Stokes respiration. It is impossible to regard the action of nitrite of amyl as being in any way different in kind.

The results following the injection of pilocarpine seem to support this view. Immediately after the shock of the injection, and before the drug could reach any of the centres, there was a cessation of the pauses; but this soon passed away, and allowed a return of the former phenomena, with this difference, that after the drug had exerted its effects, or had been allowed time enough to exert its influence, there was a shortening of the time occupied respectively by the two phases of breathing—period and pause. This effect on the respiration was of short duration, for as already mentioned, after a quarter of an hour the breathing had become entirely the same as before the administration of pilocarpine.